

Docket No.: 2059-0103US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Harold G. BROWN et al.

Application No.:

Confirmation No.:

Filed:

Examiner:

For: A PHARMACEUTICAL COMPOSITION OF
COMPLEX CARBOHYDRATES AND
ESSENTIAL OILS AND METHODS OF
USING THE SAME

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Karen K. Brown, B.S., Ph.D., do declare and say as follows:

I am a graduate of Washburn University, Topeka, Kansas and Oklahoma State University, Stillwater, Oklahoma.

My mailing address is c/o Dermal Research Laboratories, Inc., 5501 N.W. Foxhill Road, Parkville, Missouri 64152.

I am presently employed by Dermal Research Laboratories, Inc., in the position of Chief Technology Officer (Partner & Secretary).

I am listed as one of the inventors of the subject of the above-identified application. I have read and I understand the prosecution history of the present application.

I. **Cost of Low Purity vs High Purity Hyaluronic Acid**

The Examiner has indicated that there has been no evidence provided about the exorbitant costs of high purity HA. In the specification, column 13, lines 25 to 31 state "For instance, cosmetic grade hyaluronic acid which is of low purity (containing up to 5% impurities such as proteins, nucleic acids, teichoic acids and endotoxins) costs approximately \$2,000/Kg, whereas high purity pharmaceutical grade hyaluronic acid required for injection into mammals costs at least \$100,000/Kg and contains less than 0.5% impurities."

In fact, a price quote obtained in 1994 from Genzyme for medical grade hyaluronic acid (high purity as used by Della Valle and Balazs) is attached as Appendix A. A further note with comments resulting from a phone conversation is presented as Appendix B. It is noted that Sterile Medical Grade Hyaluronic Acid, the type used by Della Valle and Balazs, was quoted as costing between \$275.00/g (\$275,000/Kg) and \$350.00/g (\$350,000/Kg). At the lower cost of \$275,000/Kg a proposed daily dose of 100 mg, as described in the current application, would cost \$27.50 just for the HA (not including formulation costs, container and cap costs, labor or profit). This would mean that a month's supply would cost \$825.00 just for the HA. In comparison, the cost of low purity HA, that could not be used for injection or surgery as described in by Della Valle and Balazs and would not pass the owl monkey eye test, cost a maximum of \$2,000/Kg at the time our patent application was filed. Some was even purchased for \$1300/Kg. At this price, the cost of HA used in a 100mg daily dose would be only \$0.13 to \$0.20 (no formulation costs, bottles, caps, labor or profit). The latter is an acceptable cost for daily use.


It is noted that the current application states daily dosage. For instance, in column 25, lines 7-9 and column 25 lines 24-25 daily doses are discussed. The HA of Della Valle and Balazs is used for surgery or parenteral administration (injection) where high purity (medical grade) HA is required on a periodic basis, not daily. If one were to inject low purity HA into the eye or parenterally, it would cause damage, more than likely causing infection and inflammation. This is why both Della Valle and Balazs had to use medical grade or high purity HA. Also, this medical grade HA was not used daily but used only on rare occasions during specialized surgeries.


The Examiner rightly states that Both Balazs and Della Valle use their HA compositions in surgery and even apply them to the eyes (Della valle, Example 30, col 28-29 section II, col 32 section V; Balazs, col 14, Therapeutic Uses of Purified HUA). Application to the eyes and use in surgery requires medical grade HA (\$275,000/Kg). The low purity HA that is used in the current invention is not able to be used in surgery nor is it able to be used in the eye. Medical grade HA must pass an owl monkey eye test that is described throughout the Balazs 4,141,973 patent. This owl monkey eye test is described in detail in column 7, starting at line 63 through column 9 line 61. This is a test that determines the purity of HA and safety for medical uses such as for surgery, for use in the eye and for injection. Applicants clearly state that the low purity HA will not pass the owl monkey eye test (see column 4 lines 4-8). Therefore, the low purity of the present invention would not be able to be used by Della Valle or Balazs.

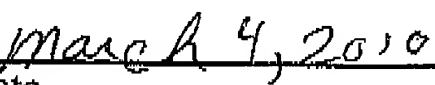
Low Purity HA Not Commercially Available at the Time of Della Valle and Balazs.

I, as one skilled in the art and working with hyaluronic acid during the late 1970s, was unable to purchase commercially available low purity HA as described in our invention. My initial work was conducted with medical grade (high purity HA). However, after realizing that my use required daily administration of HA and that medical grade (high purity) HA was not affordable, I requested that a company in France that was preparing medical grade HA, manufacture a less pure grade that would be affordable for use on a daily basis. I used that material for my oral and mucosal evaluation preparations. Therefore, as far as I am aware, at the time of Della Valle (1988) and Balazs (1979), low purity HA was not even commercially available. Both would have had to use medical grade HA. Low purity HA would not have worked for their preparations because it would not have passed the owl monkey eye test of Balazs and could not be injected or used in the eye as described by Della Valle.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.


Signature


Karen K. Brown


Date

Appendix A



GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562, U.S.A.
617-252-7500
TLX 201223 GENCMB
FAX 617-252-7600

**** FACSIMILE TRANSMISSION ****

TO: Dr. Karen Brown, Miles, Inc.
FROM: Stacy Visconti, Genzyme Corporation
RE: Hyaluronic Acid Inquiry
Pages: 4

10/12/94

Dr. Brown,

Thank you for your inquiry regarding Genzyme's Medical Grade Hyaluronio Acid.

I discussed the possibility of producing 10 - 30 Kilograms of Sterile HA powder at a molecular weight of ~500,000 daltons with our manufacturing director, Tom Offenbacher. Mr. Offenbacher said this would be feasible.

You may discuss product specifications and business development issues with Bonnie Fendrock, Director, Biotherapeutics.

If you would like to place an order for a 10 gram bottle of the material we have in stock, please contact me directly.

Attached is our fact sheet and a certificate of analysis for a lot of sterile HA powder.

I look forward to hearing from you soon.

Best Regards,

Stacy Visconti
Customer Service Representative

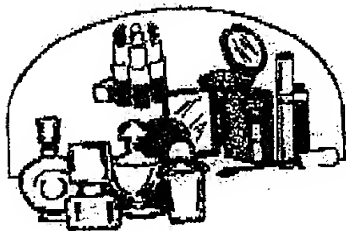
phone: 1-800-332-1042 or 617-252-7768
fax: 617-252-7759

cc: B. Fendrock

OCT-12-1994 13:09

EMULTEC

12142478226 P.01



Emultec Specialty Products, Inc.
3500 Garden Brook Drive Dallas, Tx 75234
(214) 247-7766 (214) 247-8226 Fax

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CALL THE ABOVE NUMBER.

NUMBER OF PAGES: ONE (INCLUDING THIS PAGE)

October 12, 1994

ATTN: DR. KAREN BROWN
Regarding: HYALURONIC ACID FROM GENZYME

Emultec can not sell Pharmaceutical Grade Hyaluronic Acid, you can get
this grade direct from Genzyme (1-800-326-7002). If you have any questions,
please call.

Best regards,

Jacklin S. Vetkoetter

Genzyme - Stacy Viscotti
Low MW
10 Kg/yr
Sterile 350/g bulk
10g bottle Low MW
in stock
High MW 1.0-1.7 Mc
#275,000/Kg
11:00 AM
Dr Jim Burns

TOTAL P.01